# Synthesis and Biological Evaluation of Glycosidase Inhibitors: *gem*-Difluoromethylenated Nojirimycin Analogues

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*Received January 19, 2006*

In our ongoing program aimed at the design, synthesis, and biological evaluation of novel *gem*-difluoromethylenated glycosidase inhibitors, *gem*-4,4-difluoromethylenated iminosugars (**5**−**9**) were synthesized. The biological evaluation of these synthetic iminosugars showed that the *gem*-difluoromethylenyl group generally reduced the inhibition of glycosidases. However, this was not the case at pH 5.0, where the *gem*-difluoromethylenated iminosugar **6** was a stronger inhibitor than comparable iminosugars **1** and **36**, suggesting that the influence of this group is mainly through its effect on the amine. It is proposed that the unprotonated iminosugar is the species preferably bound by $\beta$-glucosidase, due to the lower p$K_a$ value of iminosugar **6** than of **1** or **36**, leaving iminosugars **1** and **36** mostly protonated at pH 5.0, while iminosugar **6** is not. Iminosugar **6** also displayed good and selective inhibition of $\beta$-glucosidase at pH 6.8.

## Introduction

Polyhydroxylated piperidines and iminosugars play an important role in acting as strong and specific inhibitors of carbohydrate-processing enzymes (i.e. glycosidases and glycotransferases).[1] Perhaps, the best known iminosugars are the naturally occurring 1-deoxynojirimycin (DNJ) **1** and L-1-deoxyfuconojirimycin **2** (Figure 1), both of which have been demonstrated to be excellent inhibitors of glucosidase and fucosidase, respectively.[2] These iminosugars have a tremendous potential as leads for therapeutic reagents for a number of diseases,[3] due to the simple fact that glycosidases are critical for the normal cellular development of all organisms. Especially noteworthy are the biologically highly active iminosugars *N*-butyl-1-DNJ (Zavesca) **3** and *N*-hydroxyethyl-DNJ (miglitol) **4** (Figure 1), which successfully have completed clinical trials for type 1 Gaucher disease and lysosomal storage disorder.[4] However, notwithstanding extensive synthesis and investigation of highly bioactive iminosugars, a remaining drawback associated with the use of many iminosugars is their lack of selectivity for $\alpha$- and $\beta$-glycosidase inhibitors, and this has been shown to cause problems and side effects in therapeutic applications.[1a] For example, the clinical trials with *N*-butyl-DNJ have highlighted some important side effects mediated by the inhibition of glucosidases.

Modification of a known iminosugar inhibitor is a promising strategy for obtaining stronger and more selective inhibitors toward a certain glycosidase of therapeutic interest. In general, there are two main strategies for modification of iminosugars: (a) alterations of the ring hydroxyl residues or (b) introduction of different alkyl groups on the amino group. In the past decade, tremendous efforts have been devoted to the alteration of the ring hydroxyl groups, which involved protection of the hydroxyl groups,[5] substitution with other groups for the hydroxyl groups,[6] or changing the stereoconfiguration.[7] However, few studies have dealt with the effect of electron-withdrawing groups on the bioactivity, especially when electron-withdrawing groups are located in the piperidine ring. As a strong electron-withdrawing group and suggested as an isopolar and isosteric substituent for oxygen, the *gem*-difluoromethylene has been successfully used in modifying nucleosides into anticancer drugs.[8] In view of the aforementioned and the awakening comprehension of structure−activity relationships for iminosugars,[6,9] we designed and synthesized 4,4-difluoromethylenated iminosugars. The design of our target molecules was based on the following two considerations: First, the C2−OH and the C3−OH groups in an iminosugar typically are critical for a good binding to the enzymes, whereas the C4−OH group in some cases is nonessential. Second, the strongly electron-withdrawing *gem*-difluoromethylene group would greatly affect the p$K_a$ of an ammonium salt, which could have some interesting consequences, such as improved selectivity. Consequently, we wondered how the presence of a $CF_2$ group in the C4 position of the piperidine ring in nojirimycin analogues would affect the biological activity and selectivity of target molecules D-1,4-dideoxy-4,4-difluoronojirimycin **5**, D-1,4-dideoxy-4,4-difluoromannonojirimycin **6**, L-1,4-dideoxy-4,4-difluorogulonojirimycin **7**, D-1,4,6-trideoxy-4,4-difluoronojirimycin **8**, and L-1,4,6-trideoxy-4,4-difluoronojirimycin **9** (Figure 2).

## Results and Discussion

**Chemistry.** The synthesis of D-1,4-dideoxy-4,4-difluoromannonojirimycin **6**, which is presented in Scheme 1, features an efficient intramolecular cyclization to construct the piperidine ring skeleton. Starting from (*R*)-glyceraldehyde acetonide and 3-bromo-3,3-difluoropropene, diols **11** and **17** were conveniently prepared using our reported methodology.[10] Selective benzoylation of the primary hydroxyl group in diol **11** gave benzoate **12** in 90% yield. Then, treatment of compound **12** with trifluoromethanesulfonic anhydride in dichloromethane at −25 °C afforded the corresponding triflate intermediate, which directly reacted with $NaN_3$ in DMF at room temperature to give azide **13** in 89% yield. Removal of isopropylidene ketal in azide **13** with 75% acetic acid at 50 °C smoothly gave diol **14** in 96% yield. Selective mesylation of the primary hydroxyl group in diol **14** proceeded well, and desirable methanesulfonate **15**

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10.1021/jm060066q CCC: $33.50 
Published on Web 04/13/2006

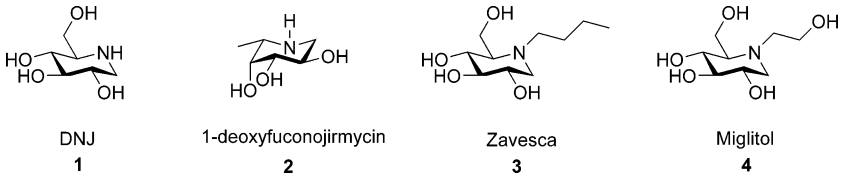



**Figure 1.** Some highly bioactive iminosugars **1**−**4**.

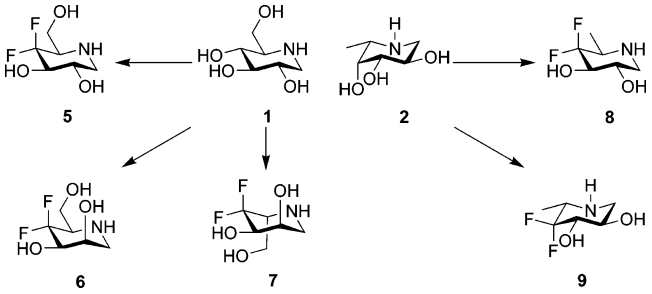


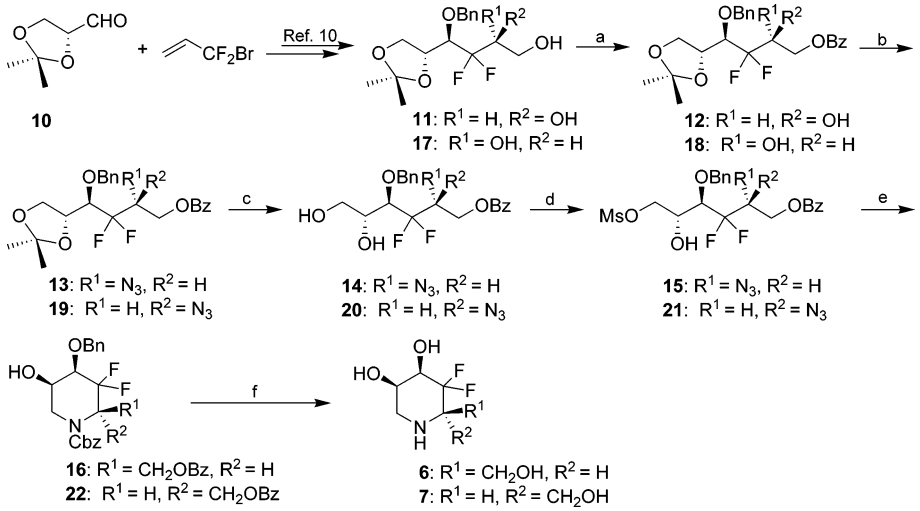

**Figure 2.** Design of *gem*-difluoromethylenated iminosugars **5**−**8**.

was obtained in 81% yield. Reduction of azide group in compound **15** with triphenylphosphine successfully afforded the corresponding piperidine, which was then directly treated with benzyloxycarbonyl chloride to give carbamate **16** in 82% overall yield. Finally, one-step removal of the benzyl group and *N*-benzyloxycarbonyl group of carbamate **16** via hydrogenation followed by deprotection of the benzoyl group with a saturated solution of ammonia in methanol gave the expected iminosugar **6** in 91% yield. Following the same procedure, iminosugar **7** was also easily prepared starting from diol **17**.

It was evident that the reversion of the center C2 in compound **6** would result in accessing iminosugar **5**. However, initial attempts to carry out the chiral inversion via the Mitsunobu reaction of piperidine **16** failed to afford the desired compound. Fortunately, we were surprised to find that the inverse configuration could be conveniently achieved prior to cyclization (Scheme 2). Selective protection of the primary hydroxyl group in diol **14** as the *tert*-butyldimethylsiyl ether **23** progressed well in 86% yield. Then, exposure of the alcohol **23** to MsCl/$Et_3N$ in $CH_2Cl_2$ at room temperature gave the mesylate **24** in 95% yield. It should be noted, about inversing the configuration at C5 in mesylate **24** via $S_N2$ nucleophilic substitution, that basic conditions should be avoided due to the strong electron-withdrawing property of the difluoromethylenyl group. It renders the neighboring hydrogen somewhat acidic and might result in racemization if basic conditions were utilized. Thus, the somewhat acidic conditions of NaOAc/$Ac_2O$ was adopted in the $S_N2$ nucleophilic reaction of compound **24**, and desired diacetate **26** was obtained in 53% yield after treatment with an excess of NaOAc in $Ac_2O$ for 36 h at 140 °C. In addition, diacetate **26** could also be provided in 74% yield by removal of the TBS protecting group of **24** with AcOH/$H_2O$/THF and subsequent treatment of resulting alcohol **25** with excess sodium acetate in $Ac_2O$ for 24 h. Then, removal of the acetyl groups in compound **26** with HCl/MeOH proceeded well to give the diol **27** in 97% yield. Finally, using the procedure as that described for synthesis of iminosugar **6** from diol **14**, compound **27** was converted into D-1,4-dideoxy-4,4-difluoronojirimycin **5**.

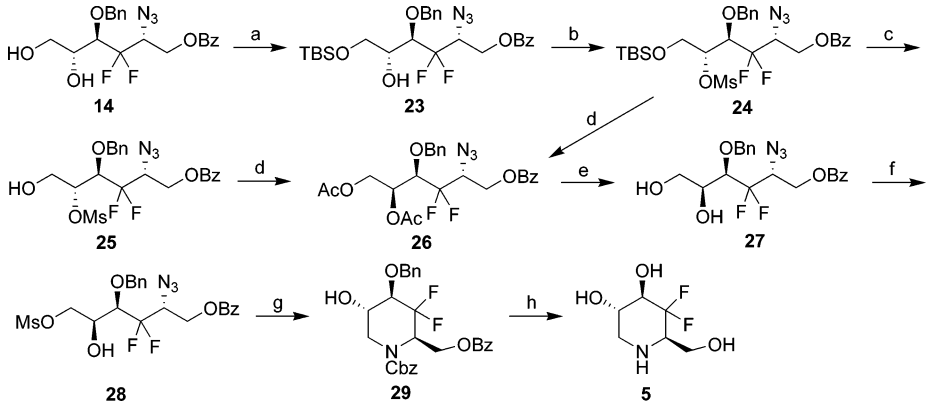
Iminosugars **8** and **9** were prepared according to our developed synthetic strategy (Scheme 3).[11] That is, Alcohol **30**, prepared from 2,2,2-trifluoroethanol,[12] was first treated with MsCl/$Et_3N$ to give mesylate **31** in 96% yield. Then, Pd(0)-catalyzed regioselective allylic substitution of **31** with $NaN_3$ afforded the desired azide **32** in 96% yield. Conversion of the azide **32** into the *N*-Cbz-amine **33** was accomplished by treatment with $PPh_3$ in dry THF followed by hydrolysis of the intermediate phosphoryl imine and addition of CbzCl. The asymmetric AD reaction of compound **33** was carried out, and diols **34** and **35** were obtained with good ee values (82−84%) and in moderate yield using $(DHQ)_2PHAL$ and $(DHQD)_2PHAL$ as the ligand, respectively. Finally, deprotection of diols **34** and **35**, followed by a highly diastereoselective hydrogenation of intermediates, gave the desired iminosugars **8** and **9**, respectively.

**Scheme 1.** Synthesis of D-1,4-Dideoxy-4,4-difluoromannonojirimycin **6** and l-1,4-Dideoxy-4,4-difluorogulonojirimycin **7** from (*R*)-Glyceraldehyde Acetonide[a]



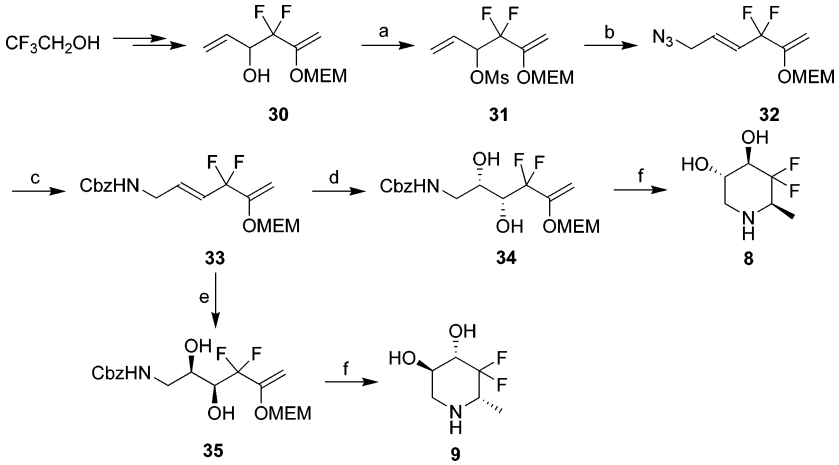

[a] Reagents and conditions: (a) BzCl, pyridine, $CH_2Cl_2$, −78 °C, 2 h; (b) (i) $Tf_2O$, pyridine, $CH_2Cl_2$, −25 °C, 3 h; (ii) $NaN_3$, DMF, rt, 10 h; (c) 75% AcOH, 50 °C, 2 h; (d) MsCl, collidine, $CH_2Cl_2$, 0 °C, 12 h; (e) (i) $PPh_3$, THF, rt, 20 h; (ii) saturated $NaHCO_3$, 65 °C, 12 h; (iii) CbzCl, rt, 3 h; (f) (i) $H_2$, $Pd(OH)_2$/C, MeOH, 1 atm, rt, 10 h; (ii) saturated $NH_3$/MeOH, rt, 36 h.

**Scheme 2.** Synthesis of D-1,4-Dideoxy-4,4-difluoronojirimycin **5** via the Inversion of Mesylate **25**[a]




[a] Reagents and conditions: (a) TBSCl, imidazole, DMF, rt, 2 h; (b) MsCl, $Et_3N$, DMAP, $CH_2Cl_2$, rt, 12 h; (c) THF/$H_2O$/AcOH (1:1:3), rt, 48 h; (d) AcOK, $Ac_2O$, 140 °C, 24 h; (e) HCl, MeOH, $CH_2Cl_2$, rt, 8 h; (f) MsCl, collidine, $CH_2Cl_2$, 0 °C, 12 h; (g) (i) $PPh_3$, THF, rt, 20 h; (ii) saturated $NaHCO_3$, 65 °C, 12 h; (iii) CbzCl, rt, 3 h; (h) (i) $H_2$, $Pd(OH)_2$/C, MeOH, 1 atm, rt, 10 h; (ii) saturated $NH_3$/MeOH, rt, 36 h.

**Scheme 3.** Synthesis of d-1,4,6-Trideoxy-4,4-difluoronojirimycin **8** and L-1,4,6-Trideoxy-4,4-difluoronojirimycin **9** from Trifluoroethanol[a]

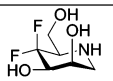
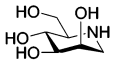
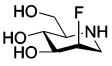
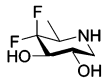
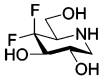
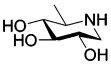
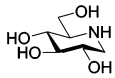
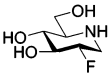
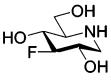
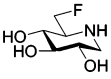
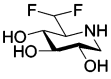



[a] Reagents and conditions: (a) MsCl, $Et_3N$, DMAP, $CH_2Cl_2$, rt, 12 h; (b) $NaN_3$, $Pd(PPh_3)_4$, THF/$H_2O$, rt, 6 h; (c) (i) $PPh_3$, THF, rt, 20 h; (ii) $H_2O$, 65 °C, 12 h; (iii) $NaHCO_3$, CbzCl, rt, 4 h; (d) AD-mix-α, $MeSO_2NH_2$, rt, 48 h; (e) AD-mix-*β*, $MeSO_2NH_2$, rt, 48 h; (f) (i) $SOCl_2$, MeOH, rt, 10 h; (ii) $H_2$, Pd/C, 80 psi, rt, 16 h.

**Enzymology.** Difluoromethylenylated iminosugars **5**−**9** were used to investigate their inhibition activities toward 10 different glycosidases, which included the *β*-glucosidase from almonds, α-glucosidase from yeast, *β*-galactosidases from *Saccharomyces fragilis* and *Aspergillus orizae*, α-galactosidase from green coffee beans, α-mannosidases from jack bean and almonds, *β*-mannosidase from snail, and the α-fucosidases from bovine kidney and human placenta. Using the corresponding nitrophenyl glycoside substrates, all assays were performed at 25 °C and pH 6.8 except the snail *β*-mannosidase assay, where pH was 4.0. Iminosugars **5**, **7**, and **8** showed no or negligible inhibition activities against all 10 enzymes at concentrations, which meant that the $K_i$ was larger than 1 mM (Table 1). Similarly compound **6** displayed no or negligible inhibition ($K_i$ was larger than 1 mM) against all the enzymes except almond *β*-glucosidase, while **9** had $K_i$ > 1 mM for all enzymes except the two fucosidases (Table 2). In addition, the inhibition of almond *β*-glucosidase by **6** and the inhibition of bovine kidney and human placenta α-fucosidase by **9** was competitive.

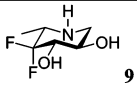
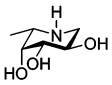
The inhibition profile of these five compounds **5**−**9** is not entirely surprising on the basis of their stereochemistry. Previous experience has shown that glycosidase inhibitors in most cases are crucially dependent on their configuration and that epimerization of a hydroxyl group away from the stereochemistry of the substrate usually decreases inhibition.[13] Therefore, the iminosugar **7**, which resembles the unnatural L-allose or L-gulose, could be expected to be the bad inhibitor of the 10 enzymes, as it was found to be. Somewhat surprising may be the observation that compound **8**, which is a 6-deoxy-D-glucose or galactose analogue, did not display any inhibition of any of glucosidases or galactosidases, but as 1,6-dideoxynojirimycin **9** has been found to be a relatively poor glycosidase inhibitor (Table 1),[6a] it is not. Even more surprising was the observation that compound **5** essentially is not an inhibitor of glucosidase or galactosidases and **6** is not an inhibitor of galactosidases. Iminosugars **6** and **9** are analogues of d-mannose and l-fucose, respectively, so in these cases inhibition of mannosidases or fucosidases could be expected and be used to evaluate the influence of displacing the 4-OH with a *gem*-difluoro group. The fluoro atom is normally expected to be able to mimic the hydrogen-bond-accepting properties of an OH, but at the same time the *gem*-difluoro group is strongly electron-withdrawing and will affect the p$K_a$ of the iminosugar profoundly. Therefore, analysis of the influence of the difluoro group is therefore complicated by these various effects. The p$K_a$ of **6** was measured to 5.3, while the p$K_a$ of 1-deoxymannonojirimycin is 7.6,[14] meaning an electron withdrawing effect of 2.3 pH units of the difluoro group. Using our p$K_a$ prediction methodology,[13,15] the p$K_a$ of compound **6** is predicted to be 5.1, which is quite close to the measured value.

**Table 1.** Inhibition Constants at 25 °C of *gem*-Difluorosugars **5**, **6**, and **8** in Comparison with Iminosugars **36**−**42**[a]

| Iminosugars | $K_i$ in $\mu$M | | | | |
|---|---|---|---|---|---|
| | β-glucosidase (almond) pH = 6.8 | β-glucosidase (almond) pH = 5.0 | α-mannosidase (almond) | α-mannosidase (Jack bean) | α-glucosidase (yeast) |
|  **6** | 45±5 | 92±7 | >1000 | >1000 | >1000 |
|  **36** | 300 | 1400 | 110 | 68 | 6.5 |
|  **37** | >1000 | - | - | - | - |
|  **8** | >1000 | >1000 | >1000 | >1000 | >1000 |
|  **5** | >1000 | - | - | - | >1000 |
|  **38** | 780 | - | - | - | 1560 |
|  **1** | 47 | 300 | - | 400 | 25 |
|  **39** | >10000 | - | - | - | 2000 |
|  **40** | >10000 | - | - | - | 2500 |
|  **41** | 600 | - | - | - | 19 |
|  **42** | - | 8700 | - | - | 7500 |

[a] Data for compounds **36**−**42** are taken from refs 6a (**1**, **37**, **38**), 16 (**1**, **36**), 17 (**1**, **36**), 18 (**39**−**41**), and 19 (**42**). −, Not available. $K_i$ in $\mu$M.

**Table 2.** Inhibition Constants at pH 6.8 and 25 °C of *gem*-Difluorosugar **9** in Comparison with Fuconojirimycin **2**[a]

| Iminosugars | $K_i$ in $\mu$M | |
|---|---|---|
| | α-fucosidase (bovine kidney) | α-fucosidase (human placenta) |
|  **9** | 570±10 | 250±10 |
|  **2** | 0.029 | 0.0013 |

[a] Data for compound **2** are taken from refs 21 and 22.

From the comparison of **6** with its 4-hydroxylated parent **36** it is seen that generally the introduction of the 4,4′-*gem*-difluoro functionality reduces binding (Table 1). Thus, while **36** is a fair to good mannosidase and α-glucosidase inhibitor, compound **6** displays no inhibition. On the other hand, **6** is, compared to **36**, a very good inhibitor of almond $\beta$-glucosidase. In fact, **6** is, despite having the wrong configuration at the 2-position, as potent as the *gluco*-configured 1-deoxynojirimycin **1** at pH 6.8 and 9-fold more potent at pH 5.0.

As is seen from the data of previously made fluorinated analogues of **1** and **36** (Table 1), it is clear that introduction of the fluorine atom at positions 2, 3, and 6 has reduced binding to $\beta$-glucosidase. The hydroxyl groups in the 2, 3, and 6 positions are known to be important for binding to almond $\beta$-glucosidase, while the 4-OH is unimportant.[18,20] Therefore, it appears, in general, that the fluorine atom cannot emulate an OH in the interaction with the enzyme, since only when the OH is unimportant can it be replaced with fluorine and activity be retained. Since the 4-OH is not crucial for binding to $\beta$-glucosidase, it is interesting that the fluorination increased binding to the enzyme, as this increase must be caused by the electron-withdrawing influence of the fluorine atoms on the p$K_a$ of the nitrogen. As **1** (p$K_a$ = 6.7) and **36** (p$K_a$ = 7.6) are largely protonated at pH 5.0 while **6** is not, the good inhibition by **6** and poor binding of **1** and **36** at this pH strongly suggest that the unprotonated iminosugar is the binding species. Furthermore, if the protonated iminosugars where the binding species, one would not expect **6** to be a stronger inhibitor than **36** at pH 6.8, because at this pH **6** contains much less protonated form and there is no reason why the protonated form of **6** should bind stronger than the protonated form of **36**. We can therefore conclude that the unprotonated iminosugar is the species preferably bound by $\beta$-glucosidase.

The binding constants of difluoroiminosugar **9** to fucosidases is shown in Table 2 and compared to the parent iminosugar **2**. While **36** is a fair inhibitor, the drop in binding when compared to the very potent inhibitor **2** is so remarkable that the 4-OH must have an important interaction with the enzymes that the *gem*-difluoro group does not have.

In summary, we designed and synthesized nojirimycin analogues *gem*-4,4-difluoromethylenated iminosugars **5**-**9**. The biological evaluation of these synthesized iminosugars showed that the strongly electron-withdrawing *gem*-difluoromethylenyl group had an important influence on the inhibition of glycosidase, which was attributed to the great change of p$K_a$ value of iminosugars resulting from the *gem*-difluoromethylenyl sub-

stituent. In addition, this research has also demonstrated that, although the *gem*-difluoromethylenyl group could not substitute for the key hydroxyl groups in iminosugar without resulting in decreased affinity, the replacement of a hydroxyl group in an iminosugar with *gem*-difluoromethylenyl group would be advantageous provided the unprotonated iminosugar is the preferred binding species.

## Experimental Section

**Chemistry.** All reactions were performed under an argon atmosphere. Glassware was dried by heating in an oven at a temperature above 125 °C for at least 6 h. Rotary evaporation was performed under reduced pressure and at maximum temperature 40 °C. High vacuum refers to a pressure of approximate 2 mmHg. Petrol refers to the fraction of light petroleum ether with bp 60−90 °C. Dichloromethane (DCM) was distilled from calcium hydride, and methanol was distilled from magnesium methoxide. All other reagents and solvents were purified by standard procedures or used as obtained from the supplier. All reactions were monitored by thin-layer chromatography (TLC). Optical rotations were measured using a Perkin-Elmer 241 polarimeter. $^1$H and $^{13}$C NMR spectra were recorded on a Bruker AM 300 or a Varian Mercury 300 instrument at room temperature. $^{19}$F NMR spectra were recorded on a Bruker AM300 spectrometer ($CFCl_3$ as outside standard and low field is positive). The following abbreviations were used for multiplicities: br = broad, s = singlet, d = doublet, t = triplet, and q = quartet, p = pentet. The signal of the solvent was used as an internal reference. Asterisk-marked shifts may be interchanged. COSY, NOESY, HMBC, and HMQC spectra were used for assignment of the NMR signals.

**(2*R*,4*R*)-2-Azido-4-*O*-benzyl-4-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-3,3-difluorobut-1-yl Benzoate (13).** Compound **12** (3.15 g, 7.19 mmol) was dissolved in dry $CH_2Cl_2$ (55 mL) and fresh distilled pyridine (4.6 mL) was added. After the resulted mixture was cooled to −35 °C, trifluoromethanesulfonic anhydride (2.23 g, 8.63 mmol) in $CH_2Cl_2$ (15 mL) was dropwise added to the mixture, and then the reaction mixture was stirred for about 2 h at about −25 °C. Water and $NaHCO_3$ aqueous solution (10 mL) were added after the mixture was warmed to the room temperature. The mixture was extracted with $CH_2Cl_2$ (15 mL) and the organic phase was dried over anhydrous $Na_2SO_4$. After filtration and removal of the solvent in vacuo, the residue was purified by silica gel chromatograpy to afford crude trifluoromethanesulfonic ester, which was directly dissolved in DMF (60 mL), and resulting solution was cooled to 0 °C by ice bath. Then, sodium azide (560 mg, 8.6 mmol) was added carefully with stirring. The reaction mixture was stirred overnight at room temperature. After that, water was added to quench the reaction. The reaction mixture was extracted with $CH_2Cl_2$ and the combined organic layer was washed with brine, dried over anhydrous $Na_2SO_4$, and concentrated in vacuo. The residue was purified by silica gel column chromatography to afford compound **13** (2.66 g, 81% yield) as a colorless oil: $[\alpha]^{20}_D$ −4.4 (*c* 1.300, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.04−8.07 (d, $J$ = 7.8 Hz, 2H), 7.58−7.63 (*t*, $J$ = 7.5 Hz, 1H), 7.45−7.50 (t, $J$ = 7.8 Hz, 2H), 7.33−7.40 (m, 5H), 5.03−5.07 (d, $J$ = 10.8, 1H), 4.74−4.83 (m, 2H), 4.50−4.62 (m, 2H), 4.05−4.39 (m, 4H), 1.49 (s, 3H), 1.40 (s, 3H); $^{19}$F NMR (282 MHz, $CDCl_3$) $\delta$ −116.39 (dd, $J$ = 27.6, 260.9 Hz, 1F), −117.62 (ddd, $J$ = 5.6, 18.6, 263.7 Hz); IR (thin film) 2989, 2113, 1730, 1603, 1454, 1270, 1115, 853, 711 cm$^{-1}$; MS *m*/*z* (ESI) 484 (M + $Na^+$). Anal. ($C_{23}H_{25}F_2N_3O_5$) C, H, N.

**(2*R*,4*R*,5*R*)-2-Azido-4-*O*-benzyl-3,3-difluoro-5,6-dihydroxyhex-1-yl Benzoate (14).** A mixture of compound **13** (1.98 g, 4.3 mmol) and 75% aqueous AcOH (20 mL) was stirred at 50 °C for 3 h. Then, the solvent was removed in vacuo. The resulted residue was dissolved in EtOAc (30 mL) and washed with aq $NaHCO_3$ (10 mL). The aqueous layer was extracted with EtOAc (20 mL). The combined organic layer was dried over $Na_2SO_4$ and concentrated in vacuo. The residue was quickly purified by silica gel column chromatography to afford compound **14** (1.72 g, 95% yield) as a colorless oil: $[\alpha]^{20}_D$ 0.9 (*c* 1.350, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.04−8.07 (d, $J$ = 7.8 Hz, 2H), 7.58−7.63 (*t*, $J$ = 7.5 Hz, 1H), 7.44−7.49 (t, $J$ = 7.8 Hz, 2H), 7.33−7.40 (m, 5H), 4.78−4.89 (m, 3H), 4.57−4.64 (m, 1H), 4.07−4.18 (m, 3H), 3.85−3.86 (d, $J$ = 4.5 Hz, 1H), 1.49 (s, 1H), 1.40 (s, 3H); $^{19}$F NMR (282 MHz, $CDCl_3$) $\delta$ −114.35 (ddd, $J$ = 5.9, 18.9, 264.0 Hz, 1F), −115.93 (ddd, $J$ = 6.2, 18.6 H, 263.7 Hz, 1F); IR (thin film) 3431, 2113, 1728, 1603, 1454, 1275, 711 cm$^{-1}$; MS *m*/*z* (ESI) 439 (M + $NH_4^+$). Anal. Calcd for $C_{20}H_{21}F_2N_3O_5$: C, 57.01; H, 5.02; N, 9.97. Found: C, 57.18; H, 5.22; N, 9.89.

**(2*R*,4*R*,5*R*)-2-Azido-4-*O*-benzyl-3,3-difluoro-5-hydroxy-6-(methylsulfonyloxy)hex-1-yl Benzoate (15).** Collidine (4.0 mL, 30 mmol) was added to a solution of the diol **14** (1.26 g, 3 mmol) in $CH_2Cl_2$ (60 mL) at room temperature. The mixture was cooled to 0 °C and MsCl (360 mg, 3.15 mmol) in $CH_2Cl_2$ (5.0 mL) was added dropwise. The reaction mixture was stirred for 20 h at 0 °C and quenched with aq $NaHCO_3$ (6 mL). The organic layer was separated and the aqueous layer was extracted with $CH_2Cl_2$ (8 mL). The combined organic layer was dried over $Na_2SO_4$ and concentrated in vacuo. The residue was purified by column chromatography to give compound **15** (1.21 g, 81% yield) as colorless oil: $[\alpha]^{20}_D$ −1.5 (*c* 0.900, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.04−8.07 (d, $J$ = 7.8 Hz, 2H), 7.56−7.66 (t, $J$ = 7.5 Hz, 1H), 7.43−7.48 (t, $J$ = 7.8 Hz, 2H), 7.33−7.40 (m, 5H), 4.71−4.92 (m, 3H), 4.14−4.62 (m, 6H), 3.03 (s, 3H); $^{19}$F NMR (282 MHz, $CDCl_3$) $\delta$ −112.4 (dm, $J$ = 264.8 Hz, 1F), −114.54 (d m, $J$ = 265.6 Hz, 1F); IR (thin film) 3511, 2115, 1725, 1603, 1452, 1275, 1177, 1115, 712 cm$^{-1}$; MS *m*/*z* (ESI) 522 (M + $Na^+$). Anal. ($C_{21}H_{23}F_2N_3O_7S$) C, H, N.

**4,4-Difluoro-6-*O*-benzoyl-3-*O*-benzyl-1,5-[(benzyloxycarbonyl)imino]-1,4,5-trideoxy-D-mannitol (16).** A solution of $PPh_3$ (635 mg, 2.65 mmol) in THF (10 mL) was dropwise added to a solution of compound **15** (1.10 g, 2.20 mmol) in THF (50 mL) at room temperature. After the starting material was consumed, saturated aq $NaHCO_3$ (10 mL) was added and the reaction mixture was stirred for 24 h at reflux. The reaction mixture was cooled to the room temperature and CbzCl (412.85 mg, 2.42 mmol) was added. The reaction mixture was stirred for further 4 h, the phases were separated, and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried over $Na_2SO_4$, and concentrated in vacuo. The residue was purified by silica gel column chromatography to afford compound **16** (922 mg, 82% yield) as a white solid: mp 84 °C; $[\alpha]^{20}_D$ 23.2 (*c* 1.400, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.89−8.00 (dd, $J$ = 7.8, 25.8 Hz, 2H), 7.51−7.56 (t, $J$ = 7.4 Hz, 1H), 7.17−7.41 (m, 12H), 4.83−5.08 (m, 5H), 4.48−4.64 (m, 2H), 3.84−4.33 (dd, $J$ = 11.1 Hz, 48.0 Hz, 1H), 3.97 (s, 1H), 3.84 (s, 1H), 3.02−3.12 (m, 1H), 2.21 (s, 1H); $^{19}$F NMR (282 MHz, $CDCl_3$) $\delta$ −102.76 (ddd, $J$ = 15.8, 55.3, 267.6 Hz, 1F), −111.18 (dd, $J$ = 93.6, 266.7 Hz, 1F); IR (thin film) 3431, 1723, 1603, 1498, 1271, 1124, 1067, 713, 699 cm$^{-1}$; MS *m*/*z* (ESI) 512 (M + $H^+$). Anal. ($C_{28}H_{27}F_2NO_6$) C, H, N.

**D-4,4-Difluoro-1,4-dideoxymannonojirimycin (6).** A solution of **16** (664 mg, 1.3 mmol) in MeOH (20 mL) was hydrogenated at atmospheric pressure and at 25 °C, using 10% $Pd(OH)_2$/C (300 mg) as the catalyst. After stirring for 24 h, the reaction mixture was filtered through Celite, and the solvent was evaporated. The residue was dissolved in a saturated solution of ammonia in methanol (25 mL) and stirred for 48 h. After removal of the solvent, the residue was purified by silica gel column chromatography to afford compound **6** (211 mg, 89% yield) as a white solid, which deliquated soon if placed in air: $[\alpha]^{20}_D$ −6.5 (*c* 1.250, $CH_3OH$); $^1$H NMR (400 MHz, MeOD) $\delta$ 3.88−3.90(m, 1H), 3.68−3.84 (m, 3H), 2.98−3.04 (dd, $J$ = 3.9, 13.8 Hz, 1H), 2.74−2.91 (m, 2H); $^{13}$C NMR (75.5 MHz, CDCl3) $\delta$ 123.52, 72.24, 70.55, 62.42, 59.68, 50.15; $^{19}$F NMR (282 MHz, $CD_3OD$) $\delta$ −112.99 (d, $J$ = 236.6 Hz, 1F), −128.05 (br, 1F); IR (thin film) 3435, 1107, 844, 807, 619 cm$^{-1}$; HRMS found 184.07798, $C_6H_{12}NO_3F_2$ requires 184.07797.

**(2*S*,4*R*)-2-Azido-4-*O*-benzyl-4-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-3,3-difluorobut-1-yl benzoate (19)** was prepared by the same procedure as described for **13** from **18** as a colorless oil: $[\alpha]^{20}_D$

15.5 (*c* 1.050, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 8.05−8.08 (d, $J$ = 8.1 Hz, 2H), 7.58−7.62 (t, $J$ = 7.5 Hz, 1H), 7.45−7.50 (t, $J$ = 7.8 Hz, 2H), 7.30−7.37 (m, 5H), 4.71−4.87 (m, 3H), 4.45−4.52 (t, $J$ = 9.3 Hz, 1H), 4.33−4.37 (m, 2H), 4.05−4.14 (m, 2H), 3.92−3.97 (t, $J$ = 12.0 Hz, 1H), 1.58 (s, 3H), 1.47 (s, 3H); $^{19}F$ NMR (282 MHz, $CDCl_3$) $\delta$ −114.41 (ddd, $J$ = 6.5, 13.8, 262.5 Hz, 1F), −116.54 (ddd, $J$ = 11.8, 16.1, 264.2 Hz, 1F); IR (thin film) 2990, 2114, 1729, 1603, 1454, 1271, 1116, 850, 712 $cm^{-1}$; MS *m*/*z* (ESI) 484 ($M + Na^+$). Anal. ($C_{23}H_{25}F_2N_3O_5$) C, H, N.

**(2*S*,4*R*,5*R*)-2-Azido-4-*O*-benzyl-3,3-difluoro-5,6-dihydroxyhex-1-yl benzoate (20)** was prepared by the same procedure as described for **14** from **19** as a colorless oil: $[\alpha]^{20}_D$ 19.6 (*c* 1.300, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 8.05−8.08 (d, $J$ = 7.8 Hz, 2H), 7.57−7.62 (t, $J$ = 7.5 Hz, 1H), 7.44−7.49 (t, $J$ = 7.2 Hz, 2H), 7.35−7.38 (m, 5H), 4.67−4.89 (m, 3H), 4.40−4.55 (m, 2H), 3.98−4.07 (m, 2H), 3.73−3.84 (m, 2H); $^{19}F$ NMR (282 MHz, $CDCl_3$) $\delta$ −113.28 (ddd, $J$ = 6.8, 14.4, 267.1 Hz, 1F), −114.75 (ddd, $J$ = 8.5, 18.9, 265.1 Hz, 1H); IR (thin film) 3433, 2115, 1727, 1603, 1454, 1275, 1116, 712 $cm^{-1}$; MS *m*/*z* (ESI) 439 ($M + NH_4^+$). Anal. ($C_{20}H_{21}F_2N_3O_5$) C, H, N.

**(2*S*,4*R*,5*R*)-2-Azido-4-*O*-benzyl-3,3-difluoro-5-hydroxy-6-(methylsulfonyloxy)hex-1-yl benzoate (21)** was prepared by the same procedure as described for **15** from **20** as a colorless oil: $[\alpha]^{20}_D$ −1.5° (*c* 0.900, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 8.07−8.10 (d, $J$ = 7.8 Hz, 2H), 7.58−7.63 (t, $J$ = 6.9 Hz, 1H), 7.45−7.50 (t, $J$ = 7.5 Hz, 2H), 7.33−7.39 (m, 5H), 4.72−4.90 (m, 3H), 4.47−4.57 (m, 3H), 4.35−4.40 (m, 1H), 4.26 (s, 1H), 4.02−4.16 (m, 1H), 3.48 (s, 1H), 3.03 (s, 3H); $^{13}C$ NMR (75.5 MHz, $CDCl_3$) $\delta$ 166.3, 136.6, 133.7, 129.9, 129.2, 128.8, 128.7, 128.6, 128.5, 121.5 (t, $J$ = 252.2 Hz), 77.27 (t, $J$ = 22.4 Hz), 75.84, 68.67, 62.54, 61.92 (t, $J$ = 23.4 Hz), 37.38; $^{19}F$ NMR (282 MHz, $CDCl_3$) $\delta$ −112.71 (dd, $J$ = 9.0 Hz, $J$ = 263.1 Hz, 1F), −114.83 (dm, $J$ = 267.6 Hz, 1F); IR (thin film) 3516, 3067, 2115, 1726, 1603, 1454, 1657, 1274, 1177, 1116, 713 $cm^{-1}$; HRMS found 522.1119, $C_{21}H_{23}N_3O_7F_2SNa$ requires 522.1117 ($M + Na^+$).

**4,4-Difluoro-6-*O*-benzoyl-3-*O*-benzyl-1,5-[(benzyloxycarbony)imino]-1,4,5-trideoxy-L-gulositol (22)** was prepared by the same procedure as described for **16** from **21** as a white solid: bp 88 °C; $[\alpha]^{20}_D$ −1.1 (*c* 11.00, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.85−7.88 (d, $J$ = 7.8 Hz, 2H), 7.55−7.61 (*m*, 1H), 7.27−7.42 (m, 12H), 5.05−5.17 (m, 3H), 4.89−4.93 (d, $J$ = 12.0 Hz, 1H), 4.74−4.78 (d, $J$ = 12.0 Hz, 1H), 4.47−4.50 (m, 1H), 4.43−4.46 (m, 1H), 4.09 (s, 1H), 3.75−3.84 (dm, $J$ = 20 Hz, 1H), 3.21−3.26 (d, $J$ = 15 Hz, 1H), 2.56 (s, 1H); $^{19}F$ NMR (282 MHz, $CDCl_3$) $\delta$ −106.53 (d, $J$ = 263.1 Hz, 1F), −108.68 (d, $J$ = 255.5 Hz, 1F); IR (thin film) 3512, 1722, 1602, 1440, 1276, 1118, 708 $cm^{-1}$; MS *m*/*z* (ESI) 512 ($M + H^+$). Anal. ($C_{28}H_{27}F_2NO_6$) C, H, N.

**L-4,4-Difluoro-1,4-dideoxygulonojirimycin (7)** was prepared by the same procedure as described for **16** from **21** as a white solid: $[\alpha]^{20}_D$ −16.7° (*c* 3.750, $CH_3OH$); $^1H$ NMR (400 MHz, MeOD) $\delta$ 3.83−3.93 (m, 3H), 3.70−3.78 (m, 1H), 3.57−3.63 (dd, $J$ = 7.2, 11.4 Hz, 1H), 3.07−3.19 (dm, $J$ = 27.0 Hz, 1H), 2.75−2.89 (m, 2H); $^{13}C$ NMR (75.5 MHz, $CDCl_3$) $\delta$ 122.19, 72.22, 69.76, 60.20, 57.31, 50.35; $^{19}F$ NMR (282 MHz, $CD_3OD$) $\delta$ −115.52 (dd, $J$ = 8.7, 251.8 Hz, 1F), −125.11 (dd, $J$ = 24.8, 251.2 Hz, 1F); IR (thin film) 3440, 3310, 1078, 998, 669, 607 $cm^{-1}$; HRMS found 184.07798, $C_6H_{12}NO_3F_2$ requires 184.07797.

**(2*R*,4*R*,5*R*)-2-Azido-4-*O*-benzyl-6-(*tert*-butyldimethylsilyloxy)-3,3-difluoro-5-hydroxyhex-1-yl Benzoate (23).** To a solution of **14** (968 mg, 2.3 mmol) in dry DMF (13 mL) were added imidazole (234 mg, 3.45 mmol) and TBSCl (380 mg, 2.5 mmol) at 0 °C, and the mixture was stirred for 1 h at 0 °C. The reaction was quenched with water (50 mL), and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over $Na_2SO_4$, and concentrated. The residue was purified by column chromatography to give **23** (1.06 g, 86%) as a clear oil: $[\alpha]^{20}_D$ 0.6 (*c* 1.450, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 8.04−8.08 (m, 2H), 7.56−7.61 (t, $J$ = 8.4 Hz, 1H), 7.44−7.47 (t, $J$ = 7.2 Hz, 1H), 7.30−7.37 (m, 5H), 4.77−4.88 (m, 3H), 4.54−4.61 (m, 1H), 4.24−4.36 (m, 1H), 4.05−4.14 (m, 2H), 3.72−3.87 (m, 2H), 2.80 (s, 1H), 0.92 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); $^{19}F$ NMR (282 MHz, $CDCl_3$) $\delta$ −114.02 (dm, $J$ = 263.7 Hz, 1F), −116.73 (dm, $J$ = 261.1 Hz, 1F); IR (thin film) 3511, 2115, 1726, 1603, 1455, 1358, 1276, 830, 713 $cm^{-1}$; MS *m*/*z* (ESI) 558 ($M + Na^+$). Anal. ($C_{26}H_{35}F_2N_3O_5Si$) C, H, N.

**(2*R*,4*R*,5*R*)-2-Azido-4-*O*-benzyl-6-(*tert*-butyldimethylsilyloxy)-3,3-difluoro-5-(methylsulfonyloxy)hex-1-yl Benzoate (24).** To a stirred solution of alcohol **23** (1.070 g, 2 mmol) in $CH_2Cl_2$ (15 mL) were added triethylamine (0.70 mL, 5 mmol), DMAP (10 mg, 0.08 mmol), and methanesulfonyl chloride (0.18 mL, 2.3 mmol) at 0 °C. The mixture was stirred for 12 h at room temperature and then the reaction was quenched with $H_2O$ (4 mL). The aqueous layer was extracted with $CH_2Cl_2$ (2 × 5 mL), and the combined organic layers were washed with brine and then dried over $MgSO_4$. After concentration in vacuo, the residue was purified by column chromatography to give compound **24** (1.14 g, 93% yield) as colorless oil: $[\alpha]^{20}_D$ −6.3° (*c* 0.700, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 8.03−8.07 (m, 2H), 7.57−7.63 (m, 1H), 7.34−7.49 (m, 7H), 5.01−5.05 (m, 1H), 4.93−4.97 (d, $J$ = 11.4 Hz, 1H), 4.84−4.87 (m, 1H), 4.70−4.74 (d, $J$ = 11.4 Hz, 1H), 4.53−4.60 (m, 1H), 4.35−4.44 (m, 1H), 4.12−4.26 (m, 1H), 3.94−4.07 (m, 2H), 3.10 (s, 3H), 0.92 (s, 1H), 0.10 (s, 3H), −0.11 (s, 3H); $^{19}F$ NMR (282 MHz, $CDCl_3$) $\delta$ −116.42 (dm, $J$ = 264.5 Hz, 1F), −117.93 (dm, $J$ = 260.0 Hz, 1F); IR (thin film) 2956, 2115, 1730, 1603, 1455, 1363, 1272, 1179, 1114, 838, 712 $cm^{-1}$; MS *m*/*z* (ESI) 631 ($M + NH_4^+$). Anal. ($C_{27}H_{37}F_2N_3O_7SSi$) C. H. N.

**(2*R*,4*R*,5*R*)-2-Azido-4-*O*-benzyl-3,3-difluoro-6-hydroxy-5-(methylsulfonyloxy)hex-1-yl Benzoate (25).** A solution of **24** (1.10 g, 1.80 mmol) in the THF/$H_2O$/AcOH (1:1:3) mixture (35 mL) was stirred at room temperature for 48 h. Then, the solvent was then removed in vacuo. The residue was dissolved in EtOAc (30 mL) and washed with aq $NaHCO_3$ (10 mL). The aqueous layer was extracted with EtOAc (20 mL). The combined organic layer was dried over $Na_2SO_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography to afford compound **25** (799 mg, 89% yield) as a colorless oil: $[\alpha]^{20}_D$ −7.99 (*c* 1.500, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 8.03−8.06 (d, $J$ = 7.8 Hz, 2H), 7.3−7.62 (m, 8H), 5.11−5.13 (t, $J$ = 2.2 Hz, 1H), 4.94−4.97 (d, $J$ = 11.1 Hz, 1H), 4.83−4.87 (m, 1H), 4.72−4.75 (d, $J$ = 10.8 Hz, 1H), 4.54−4.61 (dd, $J$ = 9.0, 11.7 Hz, 1H), 4.35−4.45 (m, 1H), 4.17−4.26 (m, 1H), 3.97−4.11 (m, 2H), 3.12 (s, 3H), 2.72 (br, 1H); $^{13}C$ NMR (75.5 MHz, $CDCl_3$) $\delta$ 166.0, 136.2, 133.6, 129.9, 129.1, 128.8, 128.7, 128.6, 128.4, 120.8 (t, $J$ = 254.5 Hz), 81.4, 77.1 (dd, $J$ = 23.7, 28.8 Hz), 75.4, 61.8, 61.5, 59.4 (dd, $J$ = 23.2, 30.3 Hz), 38.5; $^{19}F$ NMR (282 MHz, $CDCl_3$) $\delta$ −116.68 (dm, $J$ = 263.4 Hz, 1F), −117.86 (dm, $J$ = 260.9 Hz, 1F); IR (thin film) 3531, 2115, 1727, 1603, 1454, 1359, 1274, 1176, 810, 712 $cm^{-1}$; HRMS found 522.1128, $C_{21}H_{23}N_3O_7F_2SNa$ requires 522.1117.

**(2*S*,3*R*,5*R*)-5-Azido-6-*O*-benzoyl-3-*O*-benzyl-4,4-difluorohexane-1,2-diyl Diacetate (26).** A mixture of **25** (744 mg, 1.49 mmol), potassium acetate (1.46 g, 10 mol equiv), and $Ac_2O$ (60 mL) was stirred for 24 h at 140 °C. After the mixture was cooled to room temperature, the solvent was removed in vacuo. The residue was dissolved in EtOAc (30 mL) and washed with aq $NaHCO_3$ (10 mL). The aqueous layer was extracted with EtOAc (20 mL). The combined organic layer was dried over $Na_2SO_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography to afford **26** (564 mg, 75% yield) as a white solid: mp 63 °C; $[\alpha]^{20}_D$ −18.3 (*c* 1.000, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 8.03−8.06 (dd, $J$ = 8.4, 1.2 Hz, 2H), 7.57−7.62 (t, $J$ = 7.5 Hz, 1H), 7.34−7.49 (t, $J$ = 7.5 Hz, 2H), 7.33−7.44 (m, 5H), 5.49−5.55 (m, 1H), 4.76−4.86 (m, 3H), 4.55−4.61 (dd, $J$ = 12.3, 9.0 Hz, 1H), 4.40−4.44 (dd, $J$ = 3.6, 12.0 Hz, 1H), 4.11−4.27 (m, 3H), 2.07 (s, 6H); $^{19}F$ NMR (282 MHz, $CDCl_3$) $\delta$ −115.52 (dm, $J$ = 266.2 Hz, 1F), −116.67 (dm, $J$ = 264.5 Hz, 1F); IR (thin film) 3034, 2125, 1747, 1732, 1456, 1242, 1224, 1114, 749, 709 $cm^{-1}$; MS *m*/*z* (ESI) 528 ($M + Na^+$). Anal. ($C_{24}H_{25}F_2N_3O_7$) C, H, N.

**(2*R*,4*R*,5*S*)-2-Azido-4-*O*-benzyl-3,3-difluoro-5,6-dihydroxyhex-1-yl Benzoate (27).** A solution of HCl in MeOH [prepared at 0 °C from acetyl chloride (2 mL) and methanol (50 mL)] was added to a solution of compound **26** (560 mg, 1.1 mmol) in $CH_2Cl_2$ (15 mL). After stirring for 10 h at room temperature, the mixture was

evaporated to dryness. The residue was dissolved in EtOAc (20 mL), washed with brine, and then dried over $MgSO_4$. After concentration in vacuo, the residue was purified by column chromatography to give **27** (449 mg, 97% yield) as a white solid: mp 81 °C; $[\alpha]^{20}_D$ 9.4 (*c* 0.850, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.05−8.08 (m, 2H), 7.37−7.63 (m, 8H), 4.76−4.91(m, 3H), 4.58−4.65 (dd, $J$ = 12.3, 9.0 Hz, 1H), 4.26−4.38 (m, 1H), 3.94−4.02 (m, 2H), 3.65−3.67 (d, $J$ = 4.8 Hz, 1H), 2.61 (br, 1H); $^{19}$F NMR (282 MHz, $CDCl_3$) $\delta$ −113.04 (dm, $J$ = 270.4 Hz, 1F), −114.38 (dm, $J$ = 268.5 Hz, 1F); IR (thin film) 3440, 2121, 1731, 1603, 1456, 1319, 1270, 751, 711 cm$^{-1}$; MS *m*/*z* (ESI) 444 (M + $Na^+$). Anal. ($C_{20}H_{21}F_2N_3O_5$) C, H, N.

**(2*R*,4*R*,5*S*)-2-Azido-4-*O*-benzyl-3,3-difluoro-5-hydroxy-6-(methylsulfonyloxy)hex-1-yl benzoate (28)** was prepared by the same procedure as described for **15** from **27** as a colorless oil: $[\alpha]^{20}_D$ 11.2 (*c* 0.900, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.05−8.07 (dd, $J$ = 1.2, 7.5 Hz, 2H), 7.57−7.63 (*m*, 1H), 7.37−7.50 (t, $J$ = 7.5 Hz, 7H), 4.48−4.92 (m, 3H), 4.58−4.65 (m, 1H), 4.24−4.35 (m, 4H), 3.97−4.04 (m, 1H), 3.04 (s, 3H); $^{13}$C NMR (75.5 MHz, $CDCl_3$) $\delta$ 165.9, 136.2, 133.5, 129.9, 129.2, 128.8, 128.6, 128.5, 128.4, 121.0, 76.7, 75.9, 69.7, 67.3, 61.9, 60.4, 37.6; $^{19}$F NMR (282 MHz, $CDCl_3$) $\delta$ −113.06 (dm, $J$ = 269.3 Hz, 1F), −114.25 (dm, $J$ = 267.9 Hz, 1F); IR (thin film) 3513, 2115, 1726, 1603, 1454, 1357, 1275, 1177, 1117, 713 cm$^{-1}$; HRMS found 522.1119, $C_{21}H_{23}N_3O_7F_2SNa$ requires 522.1117.

**4,4-Difluoro-6-*O*-benzoyl-3-*O*-benzyl-1,5-[(benzyloxycarbony)imino]-1,4,5-trideoxy-D-glucitol (29)** was prepared by the same procedure as described for **15** from **27** as a white solid: mp 77 °C; $[\alpha]^{20}_D$ 10.3 (*c* 1.400, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.94 (br, 2H), 7.19−7.57 (m, 13H), 4.62−5.10 (m, 6H), 4.50−4.54 (d, $J$ = 11.7 Hz, 1H), 4.22 (br, 1H), 3.96 (br, 1H), 3.75 (s, 1H), 3.53−3.58 (d, $J$ = 15 Hz, 1H), 2.27 (br, 1H); $^{19}$F NMR (282 MHz, $CDCl_3$) $\delta$ −99.21 (d, $J$ = 267.2 Hz, 1F), −110.80 (dd, $J$ = 268.7 Hz, 1F); IR (thin film) 3571, 1723, 1711, 1602, 1498, 1270, 1114, 703 cm$^{-1}$; MS *m*/*z* (ESI) 512 (M + $H^+$). Anal. ($C_{28}H_{27}F_2NO_6$) C, H, N.

**D-4,4-Difluorono-1,4-dideoxyjirimycin (5)** was prepared by the same procedure as described for **6** from **29** as a white solid, which deliquated soon in air: $[\alpha]^{20}_D$ −39.2 (*c* 1.2250, $CH_3OH$); $^1$H NMR (300 MHz, MeOD) $\delta$ 3.88−3.93 (dd, $J$ = 3.9, 11.4 Hz, 1H), 3.46−3.66 (m, 3H), 3.14−3.20 (m, 1H), 2.82−2.94 (dm, $J$ = 24.0 Hz, 1H), 2.47−2.51 (t, $J$ = 10.8 Hz, 1H); $^{13}$C NMR (75.5 MHz, $CDCl_3$) $\delta$ 121.42, 77.39, 72.00, 62.57, 60.02, 51.05; $^{19}$F NMR (282 MHz, $CD_3OD$) $\delta$ −117.59 (dd, $J$ = 244.8 Hz, 1F), −134.52 (dm, $J$ = 243.9 Hz, 1F); IR (thin film) 3431, 1107, 843, 808, 619 cm$^{-1}$; HRMS found 184.0776, $C_6H_{12}NO_3F_2$ requires 184.07798.

**3,3-Difluoro-4-mesyloxy-2-(2-methoxyethoxymethoxy)hexa-1,5-diene (31).** To a stirred solution of alcohol **30** (2.02 g, 8.48 mmol) in $CH_2Cl_2$ (23 mL) were added triethylamine (3.0 mL, 21.5 mmol), DMAP (39 mg, 0.32 mmol), and methanesulfonyl chloride (0.90 mL, 11.72 mmol) at 0 °C. The mixture was stirred for 12 h at room temperature and then quenched with 10 mL of $H_2O$. The aqueous layer was extracted with $CH_2Cl_2$ (10 mL × 2), and the combined organic layers were washed with brine and then dried over $MgSO_4$. After concentration in vacuo, the residue was purified by flash column chromatography to give **31** (2.57 g, 96%) as a colorless oil: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 5.87−5.98 (m, 1H), 5.64 (br d, $J_{H-Htrans}$ = 17.4 Hz, 1H), 5.56 (br d, $J_{H-Hcis}$ = 10.5 Hz, 1H), 5.44−5.34 (m, 1H), 5.12 (s, 2H), 4.86 (d, $J$ = 3.3 Hz, 1H), 4.81−4.82 (m, 1H), 3.76−3.80 (m, 2H), 3.56 (t, $J$ = 5.1 Hz, 2H), 3.39 (s, 3H), 3.06 (s, 3H); $^{19}$F NMR (282 MHz, $CDCl_3$) $\delta$ −114.02 (d, $J$ = 10.5 Hz, 2F); IR (thin film) 2940, 1658, 1368, 1180, 1102, 998, 856 cm$^{-1}$; MS *m*/*z* (ESI) 334 (M + $NH_4^+$). Anal. ($C_{11}H_{18}F_2O_6S$) C, H.

**6-Azido-3,3-difluoro-2-(2-methoxyethoxymethoxy)hexa-1,4-diene (32).** To a stirred solution of **31** (1.03 g, 3.26 mmol) in THF (60 mL) and $H_2O$ (15 mL) were added $Pd(PPh_3)_4$ (200 mg, 5 mol %) and sodium azide (268 mg, 4.12 mmol). After stirring for 10 h at room temperature, the reaction mixture was extracted with ether (100 mL × 2) and the combined organic layers were washed with brine and then dried over $MgSO_4$. After concentration in vacuo, the residue was purified by flash column chromatography to give compound **32** (820 mg, 96%) as a clear oil: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 6.20 (d, $J_{H-Htrans}$ = 15.6 Hz, 1H), 5.96−6.04 (m, 1H), 5.12 (s, 2H), 4.80 (d, $J$ = 3.0 Hz, 1H), 4.66−4.68 (m, 1H), 3.92 (s, 2H), 3.74−3.77 (m, 2H), 3.54−3.57 (m, 2H), 3.39 (s, 3H); $^{19}$F NMR (282 MHz, $CDCl_3$) $\delta$ −101.17 (d, $J$ = 10.4 Hz, 2F); IR (thin film) 2931, 2886, 2109, 1653, 1081, 998, 853 cm$^{-1}$; MS *m*/*z* (ESI) 281 (M + $NH_4^+$). Anal. ($C_{10}H_{13}F_2N_3O_3$) C, H, N.

***N*-(Benzyloxycarbonyl)-4,4-difluoro-5-(2-methoxyethoxymethoxy)hexa-2,5-dienamine (33).** Triphenylphosphine (470 mg, 1.79 mmol) was added to a solution of **32** (400 mg, 1.52 mmol) in dry THF (24 mL). After the reaction mixture was stirred room temperature for 16 h, $H_2O$ (1.8 mL) was added, and the reaction was allowed to stir for another 16 h at 65 °C. When the reaction was cooled to room temperature, $K_2CO_3$ (320 mg, 2.30 mmol) and CbzCl (0.30 mL, 2.20 mmol) were added. After stirring at room temperature for 8 h, the reaction was extracted with ether (30 mL × 2), and the organic layers were washed with brine and dried over $MgSO_4$. After concentration in vacuo, the residue was purified by flash column chromatography to give **33** (510 mg, 90%) as a clear oil: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.35 (s, 5H), 6.17 (d, $J_{H-Htrans}$ = 17.3 Hz, 1H), 5.76−5.88 (m, 1H), 5.12 (s, 2H), 5.10 (s, 2H), 4.76 (d, $J$ = 3.3 Hz, 1H), 4.63−4.64 (m, 1H), 3.92 (s, 2H), 3.72−3.76 (m, 2H), 3.53−3.56 (m, 2H), 3.37 (s, 3H); $^{19}$F NMR (282 MHz, $CDCl_3$) $\delta$ −101.19 (d, $J$ = 10.7 Hz, 2F); IR (thin film) 3335, 2931, 1716, 1652, 1532, 1255, 852, 699 cm$^{-1}$; MS *m*/*z* (ESI) 389 (M + $NH_4^+$). Anal. ($C_{18}H_{23}F_2NO_5$) C, H, N.

**(2*R*,3*R*)-1-(Benzyloxycarbonylamino)-4,4-difluoro-5-(2-methoxyethoxymethoxy)hex-5-ene-2,3-diol (34).** To a solution of **33** (370 mg, 1.0 mmol) in *tert*-butyl alcohol (5 mL) and water (5 mL) at 0 °C were added $K_3[Fe(CN)_6]$ (987 mg, 3 mmol), $K_2CO_3$ (414 mg, 3 mmol), $(DHQ)_2PHAL$ (47 mg, 0.06 mmol), $K_2OsO_2(OH)_4$ (8.0 mg, 0.02 mmol), and $CH_3SO_2NH_2$ (95 mg, 1 mmol). After the mixture was stirred at 0 °C for 36 h, the reaction was quenched by addition of saturated aqueous $Na_2S_2O_3$. After stirring for 30 min, the resulting mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography to give a mixture of **33** and $MeSO_2NH_2$ (2:1) (260 mg, 55%) as a viscous oil in 82% ee (determined by chiral HPLC analysis on Chiralcel AD, hexane/2-propanol (90:10 v/v), 0.7 m/mL, $t_R$ (minor) = 36.5 min, $t_R$ (major) = 40.1 min): $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.35 (s, 5H), 5.27 (s, 1H), 5.08−5.16 (m, 4H), 4.86 (d, $J$ = 5.4 Hz, 1H), 4.74 (t, $J$ = 2.7 Hz, 1H), 4.09−4.12 (m, 1H), 3.85−3.93 (m, 1H), 3.75−3.78 (m, 2H), 3.54−3.57 (m, 1H); $^{19}$F NMR (282 MHz, $CDCl_3$) $\delta$ −110.65 (d, $J$ = 256.6 Hz, F), −118.44 (dd, $J$ = 19.2, 256.3 Hz); IR (thin film) 3355, 2939, 1706, 1657, 1533, 1456, 1329, 1264, 1152, 1089, 996, 699 cm$^{-1}$; MS *m*/*z* (ESI) 406 (M + $H^+$). Anal. ($2C_{18}H_{25}F_2NO_7 \cdot CH_5NO_2S$) C, H, N, S.

**(2*S*,3*S*)-1-(Benzyloxycarbonylamino)-4,4-difluoro-5-(2-methoxyethoxymethoxy)hex-5-ene-2,3-diol (35).** To a solution of **33** (590 mg, 1.6 mmol) in *tert*-butyl alcohol (8 mL) and water (8 mL) at 0 °C were added $K_3[Fe(CN)_6]$ (1580 mg, 3 mmol), $K_2CO_3$ (662 mg, 3 mmol), $(DHQD)_2PHAL$ (75 mg, 0.06 mmol), $K_2OsO_2(OH)_4$ (13.0 mg, 0.032 mmol), and $CH_3SO_2NH_2$ (152 mg, 1.6 mmol). After the mixture was stirred at 0 °C for 36 h, the reaction was quenched by addition of saturated aqueous $Na_2S_2O_3$. After stirring for 30 min, the resulting mixture was extracted with ethyl acetate (3 × 15 mL). The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography to give a mixture of **35** and $MeSO_2NH_2$ (2:1) (430 mg, 57%) as a viscous oil in 84% ee (determined by chiral HPLC analysis on Chiralcel OD, hexane/2-propanol (90:10 v/v), 0.7m/ml, $t_R$ (major) = 30.4 min, $t_R$ (minor) = 33.5 min): $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.36 (s, 5H), 5.28 (s, 1H), 5.08−5.14 (m, 4H), 4.86 (d, $J$ = 3.3 Hz, 1H), 4.73 (t, $J$ = 2.7 Hz, 1H), 4.09−4.13 (m, 1H), 3.84−3.92 (m, 1H), 3.74−3.77 (m, 2H), 3.53−3.55 (m, 2H), 3.44−3.51 (m, 2 H), 3.37 (s, 3 H), 3.26−3.35 (m, 1 H), 3.10 (s, 1.5 H), 3.00 (s, 1 H); $^{19}$F NMR (282 MHz, CDCl3) $\delta$ −110.65 (d, $J$ = 256.6 Hz, 1F), −118.44 (dd, $J$ = 19.2, 256.3 Hz, 1F); IR (thin film) 3358, 2939, 1707, 1656, 1533, 1330, 1265, 1151,

1094, 996, 699 $cm^{-1}$; MS *m/z* (ESI) 406 ($M + H^+$). Anal. ($2C_{18}H_{25}F_2NO_7 \cdot CH_5NO_2S$) C, H, N.

**4,4-Difluoro-1,4,6-trideoxynojirimycin (8).** Thionyl chloride (0.09 mL, 1.23 mmol) was added slowly to a cooled solution (0 °C) of **34** (190 mg, 0.60 mmol) in methanol (10 mL). The reaction mixture was allowed to stir overnight at room temperature. The methanol was removed in vacuo, and the residue was resolved in ethyl acetate (20 mL) and washed with saturated aqueous $K_2CO_3$. After concentration in vacuo, the residue was mixed with 10% Pd/C (80 mg) in methanol (8 mL) and hydrogenated under 80 psi of $H_2$ (12h). Then, the reaction mixture was filtered through Celite, and the filtrate was evaporated to give a residue. The residue was purified by flash column chromatography to give **8** (53 mg, 53%) as a white solid. This product was recrystalized from $CH_3OH$/AcOEt (1:10) to give optically pure **8**: mp 178−180 °C; $[\alpha]^{20}_D$ +30.2 (*c* 0.350, $CH_3OH$); $^1H$ NMR (300 MHz, $CD_3OD$) $\delta$ 3.50−3.64 (m, 2H), 3.38 (d, $J = 11.7$ Hz, 1H), 3.06−3.13 (q, 1H), 2.83−2.96 (m, 1H), 2.48−2.56 (q, 1H), 1.21 (d, $J = 6.2$ Hz, 3H); $^{19}F$ NMR (282 MHz, $CD_3OD$) $\delta$ −116.67 (dd, $J = 3.4$, 241.7 Hz, 1F), −138.70 (dm, 243.4 Hz, 1F); IR (thin film) 3327, 3254, 1232 1065, 1027, 820, 689 $cm^{-1}$; MS *m/z* (ESI) 168 ($M + H^+$). Anal. ($C_6H_{11}F_2NO_2$) C, H, N.

L-**4,4-Difluoro-1,4,6-trideoxynojirimycin (9).** Thionyl chloride (0.06 mL, 0.86 mmol) was added slowly to a cool solution (0 °C) of **35** (130 mg, 0.40 mmol) in methanol (8 mL). The reaction mixture was allowed to stir overnight at room temperature. Methanol was removed in vacuo, and the residue was resolved in ethyl acetate (15 mL) and washed with saturated aqueous $K_2CO_3$. After concentration in vacuo, the residue was mixed with 10% Pd/C (60 mg) in methanol (6 mL) and hydrogenated under 80 psi of $H_2$ (12 h). Then, the reaction mixture was filtered through Celite, and the filtrate was evaporated to give a residue. The residue was purified by flash column chromatography to give **9** (32 mg, 46%) as a white solid. This product was recrystallized from $CH_3OH$/AcOEt (1:10) to give optically pure **9**: mp 179−182 °C; $[\alpha]^{20}_D$ −30.2 (*c* 0.550, $CH_3OH$); $^1H$ NMR (300 MHz, $CD_3OD$) $\delta$ 3.41−3.58 (m, 2H), 3.26−3.31 (m, 1H), 2.96−3.04 (m, 1H), 2.74−2.88 (m, 1H), 2.37−2.46 (m, 1H), 1.21 (d, $J = 6.2$ Hz, 3H); $^{13}C$ NMR (75.5 MHz, $CD_3OD$) $\delta$ 119.8 (t, $J_{C-F} = 247.9$ Hz), 75.56 (t, $J_{C-F} = 19.9$ Hz), 70.53 (d, $J_{C-F} = 7.9$ Hz), 54.39 (t, $J_{C-F} = 23.7$ Hz), 49.28, 10.81 (d, $J_{C-F} = 6.3$ Hz); $^{19}F$ NMR (282 MHz, $CD_3OD$) $\delta$ −117.69 (dd, $J = 3.7$, 246.7 Hz, 1F), −138.69 (dm, $J = 244.8$, 1F); IR (thin film) 3323, 3254, 1232, 1065, 1027, 821, 688 $cm^{-1}$; HRMS found 190.0652, $C_6H_{11}NO_2F_2Na$ requires 190.0650.

**Enzyme Inhibition**. Each glycosidase assay was performed by preparing eight 2-mL samples in cuvettes, containing 1 mL of sodium phosphate buffer (0.1 M) of pH 6.8 or acetate buffer of pH 4.0, along with 0.04−0.80 mL of different substrate. The concentration of the substrate was in the range from $0.25K_M$ to $5K_M$. The substrates used were 2-nitrophenyl-$\beta$-D-galactopyranoside, 4-nitrophenyl-$\alpha$-D-galactopyranoside, 4-nitrophenyl-$\beta$-D-glucopyranoside, 4-nitrophenyl-$\alpha$-D-glucopyranoside, 4-nitrophenyl-$\alpha$-L-fucopyranoside, 4-nitrophenyl-$\alpha$-D-mannopyranoside, or 4-nitrophenyl-$\beta$-D-mannopyranoside. Also added was 0.02−0.1 mL of a solution of either the inhibitor or water, and finally each cuvette was filled up to a total volume of 1.9 mL with distilled water. Seven of the samples contained the inhibitor at a fixed concentration but with varying concentrations of nitrophenyl glycoside. The other seven samples contained no inhibitor but also varying concentrations of nitrophenyl glycoside. Finally, the reaction was started by adding 0.1 mL of a diluted solution of enzyme solution. The formation of 4- or 2-nitrophenol was monitored for 2 min at 25 °C by measurement of the absorbance at 400 nm. In the case of the $\beta$-mannosidase assay, the velocity of substrate hydrolysis was measured by quenching 200 $\mu$L of solution with 1800 $\mu$L of borate buffer (1.0 M, pH 9) every 30 s over 3 min and then measuring absorbance at 400 nm. Initial velocities were calculated from the slopes from each reaction and used to construct two Hanes plots ([S]/$v$ vs [S]), one with and one without inhibitor, which also was used to check whether inhibition was competitive. From the two Michaelis−Menten constants, $K_M$ and $K_{M'}$, thus obtained, the inhibition constant, $K_i$, was calculated. All assays were performed at pH 6.8 and 25 °C except the $\beta$-mannosidase assay, which was performed at pH 4.0. The inhibition constants ($K_i$) were obtained from the formula $K_i = [I]/(K_{M'}/K_M - 1)$, where $K_{M'}$ and $K_M$ are Michaelis−Menten constants with and without inhibitor present.

**Acknowledgment.** We thank the National Natural Science Foundation of China, Ministry of Education of China and Shanghai Municipal Scientific Committee for funding this work.

**Supporting Information Available:** Elemental analyses data of compounds and $^1H$ and $^{13}C$ NMR spectra for all the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

## References

(1) (a) Butters, T. D.; Dwek, R. A.; Platt, F. M. Inhibition of glycosphingolipid biosynthesis: Application to lysosomal storage disorders. *Chem. Rev.* **2000**, *100*, 4683−4696. (b) Sears, P.; Wong, C.-H. Carbohydrate mimetics: A new strategy for tackling the problem of carbohydrate-mediated biological recognition. *Angew. Chem., Int. Ed.* **1999**, *38*, 2301−2324.

(2) (a) Reese, E. T.; Parrish, F. W.; Ettlinger, M. Nojirimycin and D-glucono-1,5-lactone as inhibitors of carbohydrases. *Carbohydr. Res.* **1971**, *18*, 381−388. (b) Fleet, G. W. J.; Shaw, A. N.; Evans, S. V.; Fellows, L. E. F. Synthesis from D-glucose of 1,5-dideoxy-1,5-imino-L-fucitol, a potent $\alpha$-L-fucosidase inhibitor. *J. Chem.* Soc., *Chem. Commun.* **1985**, 841−842.

(3) (a) Karpas, A.; Fleet, G. W. J.; Dwek, R. A.; Petursson, S.; Namgoong, S. K.; Ramsden, N. G.; Jacob, G. S.; Rademacher, T. W. Aminosugar derivatives as potential anti-human immunodeficiency virus agents. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 9229−9233. (b) Goss, P. E.; Baker, M. A.; Carver, J. P.; Dennis, J. W. Inhibitors of carbohydrate processing: A new class of anticancer agents. *Clin. Cancer Res.* **1995**, *1*, 935−944. (c) Karlsson, G. B.; Butters, T. D.; Dwek, R. A.; Platt, F. M. Effects of the imino sugar *N*-butyldeoxynojirimycin on the *N*-glycosylation of recombinant gp120. *J. Biol. Chem.* **1993**, *268*, 570−576.

(4) Butters, T. D.; Dwek, R. A.; Platt, F. M. Therapeutic applications of imino sugars in lysosomal storage disorders.*Curr. Top. Med. Chem.* **2003**, *3*, 561−574.

(5) van den Broek, L. A. G. M.; Vermaas, D. J.; van Kemenade, F. J.; Tan, M. C. C. A.; Rotteveel, F. T. M.; Zandberg, P.; Butters, T. D.; Miedema, F.; Ploegh, H. L.; van Boeckel, C. A. A. Synthesis of oxygen-substituted *N*-alkyl 1-deoxynojirimycin derivatives: Iminosugar $\alpha$-glucosidase inhibitors showing antiviral (HIV-1) and immunosuppressive activity. *Rec. Trav. Chim. Pays-Bas* **1994**, *113*, 507−516.

(6) (a) Kajimoto, T.; Liu, K. K.-C.; Pederson, R. L.; Zhong, Z.; Ichikawa, Y.; Porco, J. A., Jr.; Wong, C.-H. Enzyme-catalyzed aldol condensation for asymmetric synthesis of iminosugars: Synthesis, evaluation, and modeling of glycosidase inhibitors. *J. Am. Chem. Soc.* **1991**, *113*, 6187−6196. (b) Arnone, A.; Bravo, P.; Donadelli, A.; Resnati, G. Asymmetric synthesis of fluorinated analogs of 1-deoxynojirimycin. *J. Chem. Soc., Chem. Commun*. **1993**, 984−986. (c) Lee, C.-K.; Jiang, H.; Koh, L. L.; Xu, Y. Synthesis of 1,3-dideoxy-3-fluoronojirimycin. *Carbohydr. Res.* **1993**, *239*, 309−315. (d) Reymond, J. L.; Pinkerton, A. A.; Vogel, P. Total, asymmetric synthesis of (+)-castanospermine, (+)-6-deoxycastanospermine, and (+)-6-deoxy-6-fluorocastanospermine. *J. Org. Chem.* **1991**, *56*, 2128−2135. (e) Kilonda, A.; Compernolle, F.; Hoornaert, G. J. Synthesis of 2-azido-6-amino and 2-fluoro-6-amino analogs of 1-deoxynojirimycin. *J. Org. Chem.* **1995**, *60*, 5820−5824. (f) Kiess, F.-M.; Poggendorf, P.; Picasso, S.; Jaeger, V. Nitro compounds. 6. Synthesis of iminopolyols via Henry reaction: A short route to the $\alpha$-mannosidase inhibitor 1,4-dideoxy-1,4-imino-d-mannitol and to amino analogs. *Chem. Commun* **1998**, 119−120.

(7) (a) Takahata, H.; Banba, Y.; Ouchi, H.; Nemoto, H. Concise and highly stereocontrolled synthesis of 1-deoxygalactonojirimycin and its congeners using dioxanylpiperidene, a promising chiral building block. *Org. Lett.* **2003**, *5*, 2527−2529. (b) Kato, A.; Kato, N.; Kano, E.; Adachi, I.; Ikeda, K.; Yu, L.; Okamoto, T.; Banba, Y.; Ouchi, H.; Takahata, H.; Asano, N. Biological properties of d- and l-1-deoxy-aza-sugars. *J. Med. Chem.* **2005**, *48*, 2036−2044.

(8) (a) Hertel, L. W.; Kroin, J. S.; Misner, J. W.; Tustin, J. M. Synthesis of 2-deoxy-2,2-difluoro-D-ribose and 2-deoxy-2,2′-difluoro-D-ribofuranosyl nucleosides. *J. Org. Chem.* **1988**, *53*, 2406−2409. (b) Hertel, L. W.; Boder, G. B.; Kroin, J. S.; Rinzel, S. M.; Poore, G. A.; Todd, G. C.; Grindey, G. B. Evaluation of the antitumor activity of gemcitabine (2′,2′-difluoro-2′-deoxycytidine). *Cancer Res.* **1990**, *50*, 4417−4722.

(9) Butters, T. D.; van den Broek, L. A. G. M.; Fleet, G. W. J.; Krulle, T. M.; Wormald, M. R.; Dwek, R. A.; Platt, F. M. Molecular requirements of imino sugars for the selective control of N-linked glycosylation and glycosphingolipid biosynthesis. *Tetrahedron: Asymmetry* **2000**, *11*, 113−124.
(10) Zhang, X.; Xia, H.; Dong, X.; Jin, J.; Meng, W.-D.; Qing, F.-L. 3-Deoxy-3,3-difluoro-D-arabinofuranose: First stereoselective synthesis and application in preparation of *gem*-difluorinated sugar nucleosides. *J. Org. Chem.* **2003**, *68*, 9026−9033.
(11) Wang, R.-W.; Qing, F.-L. Highly stereocontrolled synthesis of *gem*-difluoromethylenated iminosugars: D- and L-1,4,6-Trideoxy-4,4-difluoronojirimycin. *Org. Lett.* **2005**, *7*, 2189−2192.
(12) (a) Patel, S. T.; Percy, J. M.; Wilkes, R. D. New fluorine-containing building blocks from trifluoroethanol. *Tetrahedron* **1995**, *33*, 9201−9216. (b) Patel, S. T.; Percy, J. M.; Wilkes, R. D. [2,3]-Wittig rearrangements of difluoroallylic ethers. A facile entry to highly functionalized molecules containing a $CF_2$ group. *J. Org. Chem.* **1996**, *61*, 166−173.
(13) (a) Stütz, A. *Iminosugars as glycosidase inhibitors*. Wiley-VCH Weinheim **1999**. (b) Lillelund, V. H.; Liang, X.; Jensen, H. H.; Bols, M. Recent developments of transition-state analogue glycosidase inhibitors of non-natural product origin. *Chem. Rev.* **2002**, *102*, 515−553.
(14) Jensen, H. H.; Lyngbye, L.; Jensen, A.; Bols, M. Stereoelectronic substituent effects in polyhydroxylated piperidines and hexahydropyridazines. *Chem. Eur. J.* **2002**, *8*, 1218−1226.
(15) Bols, M.; Liang, X.; Jensen, H. H. Equatorial contra axial polar substituents. The relation of a chemical reaction to stereochemical substituent constants. *J. Org. Chem.* **2002**, *67*, 8970−74.
(16) Dong, W.; Jespersen, T. M.; Skrydstrup, T.; Bols, M.; Sierks, M. R. Valuation of isofagomine and its derivatives as potent glycosidase inhibitors. *Biochemistry* **1996**, *35*, 2788−95.
(17) Merrer, Y. L.; Poitout, L.; Depezay, J.-C.; Dosbaa, I.; Geoffroy, S.; Foglietti, M.-J. Synthesis of aza sugars as potent inhibitors of glycosidases. *Bioorg. Med. Chem.* **1997**, *5*, 519−533.
(18) Andersen, S. M.; Ebner, M.; Ekhart, C. W.; Gradnig, G.; Legler, G.; Lundt, I.; Stütz, A.; Withers, S. G. Two isosteric fluorinated derivatives of the powerful glucosidase inhibitors. *Carbohydr. Res.* **1997**, *301*, 155−166.
(19) Szarek, M. A.; Wu, X.; Szarek, W. A. Synthesis and evaluation of 1,5,6-trideoxy-6,6-difluoro-1,5-imino-D-glucitol (1,6-dideoxy-6,6-difluoronojirimycin) as a glucosidase inhibitor. *Carbohydr. Res.* **1997**, *299*, 165−170.
(20) Jensen, H. H.; Jensen, A.; Hazell, R.; Bols, M. Synthesis and investigation of L-fuco- and D-glucurono-azafagomine. *J. Chem. Soc., Perkin Trans 1* **2002**, 1190−1198.
(21) Dumas, D. P.; Kajimoto, K.; Liu, K. C.; Wong, C.-H.; Berkowitz, D. B.; Danishefsky, S. J. Iminosugar and glycal inhibitors of α-L-fucosidase. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 33−36.
(22) Legler, G.; Stütz, A.; Immich, H. Synthesis of 1,5-dideoxy-1,5-imino-D-arabinitol (5-nor-L-fuco-1-deoxynojirimycin) and its application for the affinity purification and characterization of α-L-fucosidase. *Carbohydr. Res.* **1995**, *272*, 17−30.

JM060066Q